CHAPTER 1

A brief introduction to pyrimidine chemistry: History and importance

1.1 Introduction & early history

Research towards the design, synthesis and application of bioactive molecules has always been considered as an exciting and never ending area of research. Researchers from various fields of chemistry like synthetic chemists, medicinal chemists, and theoretical chemists as well as biologists have come forward to put their hands and ideas together to discover new potential bioactive molecules. In this regard, the bioactive molecule, pyrimidine as chemical entity occupies a cardinal position. This is mainly due to the inherent bioactivity associated with such molecules and subsequent possible synthetic manipulation through various tactics. Although, the moiety is mainly known for its biological significance, its importance in the field of material chemistry can never be underestimated as lots of pyrimidine derivatives are reported recently as constituent of liquid crystal, fluorescence material, photo responsive surfaces etc. attracting the attention of material chemist also.

Since the discovery, as an important constituent of nucleic acids, pyrimidines have been occupying a distinct and unique place in human's life and consequently in organic and medicinal chemistry research. The core molecule pyrimidine is a member of diazine family (isomeric to pyridazine and pyrazine, **Fig. 1**) having two

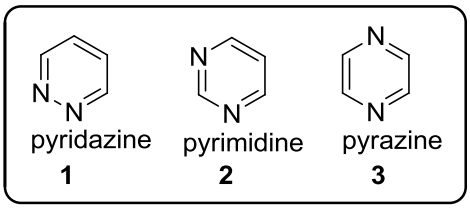


Fig.1: Three isomeric diazines

nitrogen atoms at position 1 and 3 of the six membered ring. The numbering of atoms in the ring had been done in the way (A), before IUPAC proposed another way (B), which has been later accepted and used universally (**Fig. 2**) [1].

The resonance structures of pyrimidine can be drawn as in **Fig. 3** which suggests that electron density is maximum at C-5 position, although attack towards electron

deficient centre is difficult as the pyrimidine ring on the whole is deactivated. However, attack via position 5 to electrophiles takes when an electron releasing group (viz. -OH, -NH_2) is present at any of the 2, 4 and 6 position (**Fig. 4**).

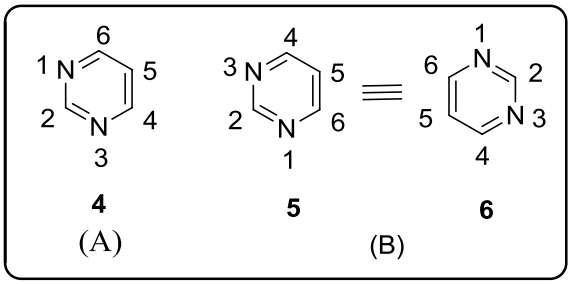


Fig.2: Numbering of atoms in pyrimidine moiety

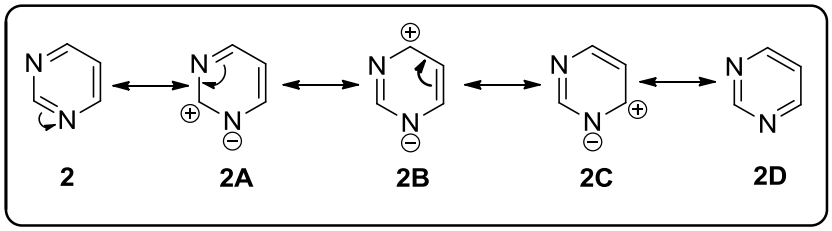


Fig. 3: Resonance in pyrimidine

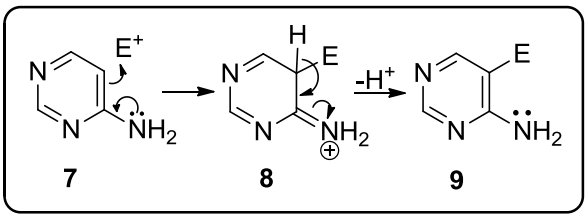


Fig. 4: Electrophilic attack at 5-position of pyrimidine ring

The first report in pyrimidine chemistry is found published in 1776 when C. W. Scheele isolated uric acid (**10**), a purine derivative (one ring of which is a pyrimidine) in pure form (**Fig. 5**) from urinary *calculie* (stones) [2].However, it needed another 42 years to isolate the first pyrimidine derivative alloxan(**11, Fig. 5**) by Brugnatelli in 1818 [3].The first laboratory synthesis of pyrimidine derivative was carried out in 1879, when Grimaux prepared barbituric acid (**14**)from urea (**12**) and malonic acid (**13**) in presence of phosphoryl chloride [4].The actual systematic study of pyrimidine started with the work of Pinner, who

synthesized pyrimidine derivatives by condensing ethyl acetoacetate with amidines in 1884 [5]. Moreover, he was the person to coin the term 'pyrimidine' to the unsubstituted parent body by combining the term 'pyridine' and 'amidine'. The parent compound was first synthesized by Gabriel in 1900, by conversion of barbituric acid (**14**) to 2,4,6-trichloropyrimidine (**15**) followed by reduction using zinc dust in hot water (**Scheme 1**) [6, 1]. Lots of other methods were developed subsequently to synthesize the core unit, and the design, synthesis and application of simple as well as annelated pyrimidine derivatives has become a field of research with immense importance and potential.

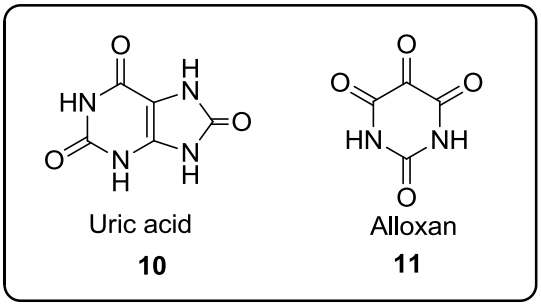
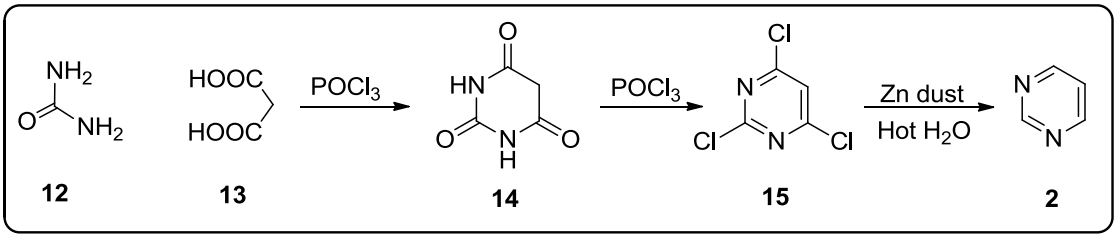


Fig. 5: Structures of uric acid and alloxan



Scheme 1: First synthesis of pyrimidine core unit

1.2 Natural abundance

Pyrimidines have a wide natural occurrence, the most important of which is the presence of pyrimidine ring as a constituent of nucleic acid. All the five most important nucleobases contain a pyrimidine unit either in a monocyclic or in a fused bicyclic system. While cytosine (**16**), thymine (**17**) and uracil (**18**) are pyrimidine nucleobases, adenine (**19**) and guanine (**20**) are two purine nucleobases, a part of which is a pyrimidine unit (**Fig. 6**). Among the three

pyrimidine bases, cytosine is found in both DNA & RNA, thymine is found in DNA and uracil is found in RNA. However, some *t*-RNA contains both thymine and uracil. These molecules can form H-bonds and do so with their complementary purine bases, which is the main binding force of the secondary structure of nucleic acids. There are three possible H-bonds between cytosine and guanine, while there are

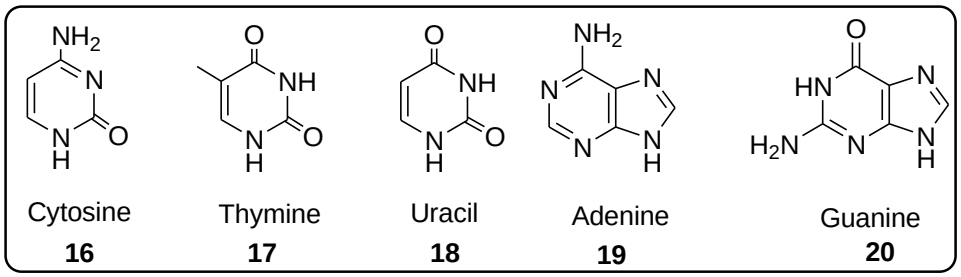


Fig. 6: Five important nucleobases

only two in between thymine; adenine as well as uracil; adenine. (**Fig. 7)**. A. Kossel, Nobel laurete in Medicine in 1910 for his contribution to the knowledge of cell chemistry made through his work on proteins, including the nucleic substances was associated with the isolation and synthesis of all the three pyrimidine nucleobases thymine, cytosine and uracil. Thymine was isolated from hydrolyzates of bovine thymus in 1893 [7], while it took another eight years for laboratory synthesis. Cytosine was first isolated in 1894 from hydrolysis of calf thymus [8]

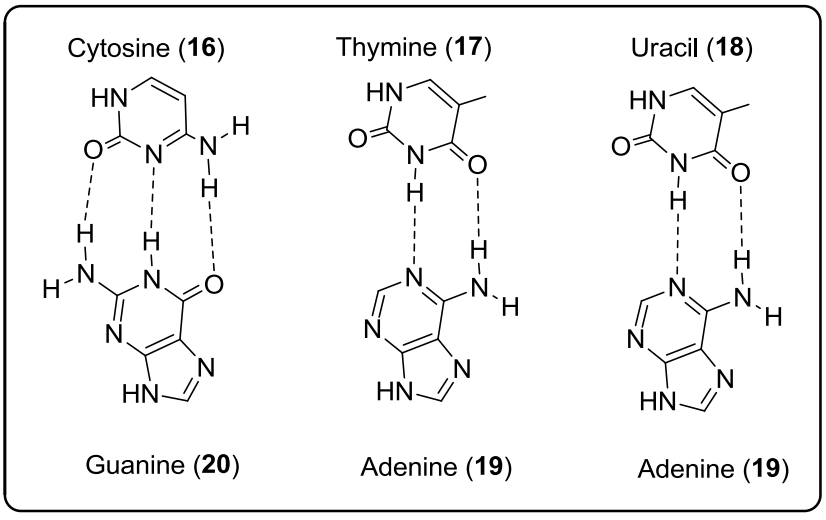
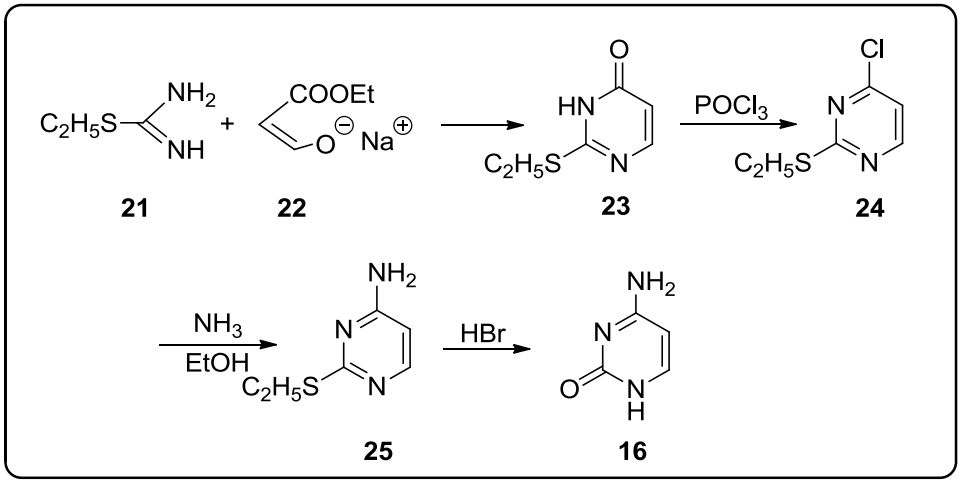
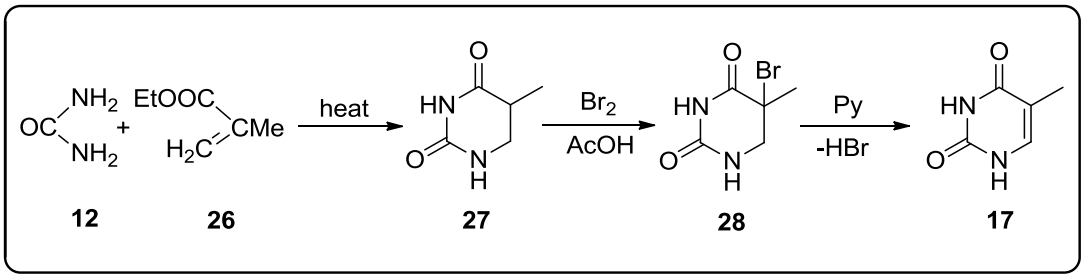


Fig. 7: Intermolecular H-bonding in nucleic acids

and by 1903, its structure was confirmed by synthesis [9]. Isolation of uracil was first performed by the hydrolysis of herring sperm in 1900 [10] while its structure was established in 1901 by synthesis. **Scheme 2**, **Scheme 3** and **Scheme 4** demonstrate three classical synthesis for cytosine, thymine and uracil respectively.



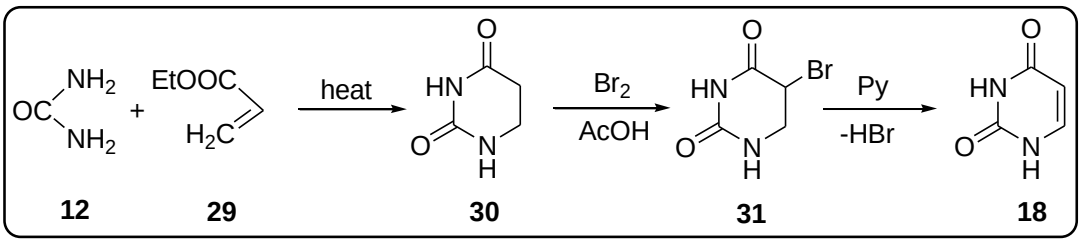
Scheme 2: Wheeler and Johnson synthesis of cytosine (1903)



Scheme 3: Fischer and Roeder synthesis of thymine (1901)

Apart from the presence as an important constituent in nucleic acid, pyrimidine derivatives are found in plant as well as animal and available in amino acids, vitamins, alkaloids etc. The most common example is caffeine (**32**), the stimulating agent present in tea and coffee. Willardiine (**33**), a non-proteinogenic L-α-amino acid was isolated from the seeds of *Acacia willardiana* [11] and later from other species of *Acacia*[12]. Thiamine (**34**) or Vitamine B_1, the anti-beriberi vitamin is a pyrimidine containing vitamin, first isolated in 1926 [13] by Jansen and Donath from rice bran and is known only in the form of salt. Bacimethrin (**35**), a naturally

occuring thiamine antimetabolite, first isolated from Bacillus megatherium is the simplest pyrimidine antibiotic [14]. In Taipei folk medicine, a plant named *Heterostemma brownii* is used for treatment of cancer, from which three pyrimidine alkaloids, heteroamines F, G and H (**36**, **37** & **38** in **Fig. 9**)were isolated in 1997. These compounds are found to be cytotoxic to several cancer cell lines [15]. Lots of other pyrimidine bearing molecules have been extracted from their medicinally important natural resources and the extracted products are also established to posses various biological activity [16].



Scheme 4: Fischer and Roeder synthesis of uracil (1901)

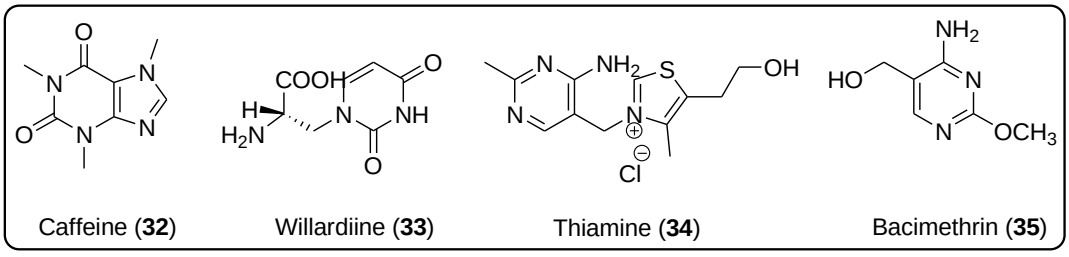


Fig. 8: Pyrimidines extracted from plant origin

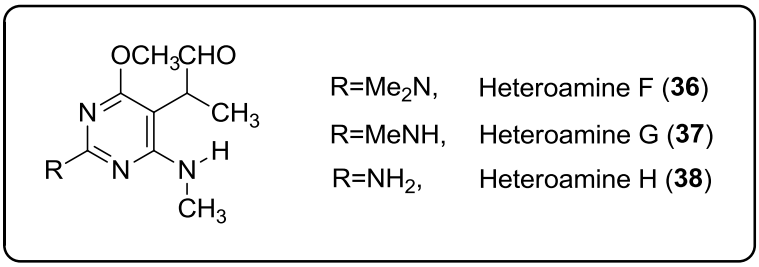


Fig. 9: Structures of three pyrimidine alkaloids

1.3 Medicinal and biological significances of pyrimidine derivatives

Along with these naturally occurring biologically important pyrimidine derivatives,

numerous reports have been published documenting the design and synthesis of wide variety of pyrimidine derivatives as well as their screening and application to address various pharmacological issues. Moreover, a large number of pyrimidine drugs are in clinical and trial use whereas numerous others have been proposed and under research to treat various threats to human life. Numerous other life-saving drugs have already been available in the market; a partial list of which has been published recently [17]. Simple examples include *5-Iodo-2'-deoxyuridine (IDU)* (**39**), which has been used as anti-herpes virus drug and *Zidovudine* (**40**), the first U.S. government-approved drug for HIV, prescribed under the names *Retrovir* and *Retrovis*. In fact, *Zidovudine* is included in the World Health Organization's Model List of Essential Medicines, which suggests the minimum medicinal needs for a basic health care system. VIAGRA® (**41**), the much talked molecule in present day's world, which is widely used in oral therapy of erectile dysfunction is the

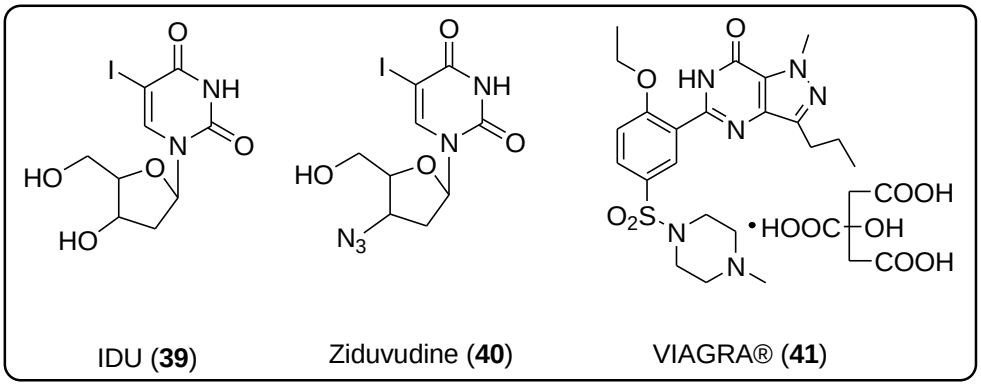


Fig. 10: Some pyrimidine based marketed drugs

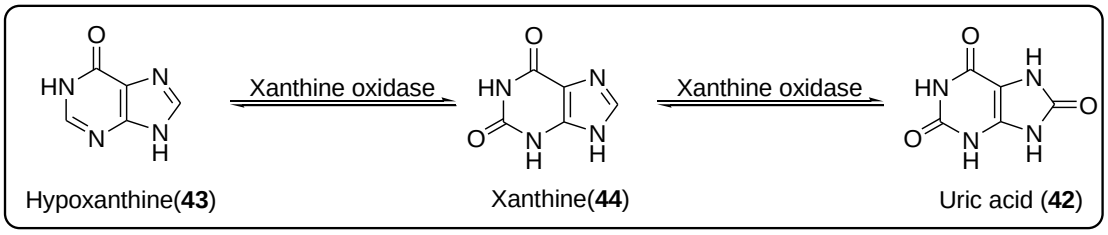
citrate salt of *sildenafil*, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phospodiesterase type 5 (PDE5). Here, we will make a humble effort to highlight some of the important bioactivities associated with pyrimidine compounds in the following few pages.

1.3.1 Treatment of gout

Gout is the clinical term describing the physiological consequences accompanying excessive uric acid (**42**) accumulation in body fluids [18]. The most common

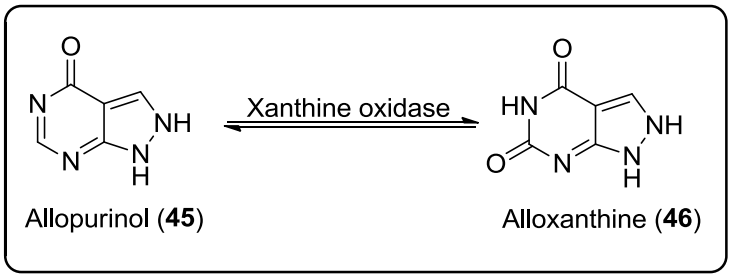
symptom of gout is arthritic pain in the joints as a result of urate deposition in cartilaginous tissue.

During the process of degradation of Adenosine monophosphate (AMP), hypoxanthine (**43**) is produced, which is further oxidized to xanthine (**44**) and then to uric acid (**42**) by the enzyme xanthine oxidase (**Scheme 5**). Uric acid loses a proton at physiological pH to form urate, which is the final product of purine degradation in human beings and is excreted through urine [19]. A high serum level of urate (hyperuricemia) is responsible for the painful joint disease 'gout'. The small joint at the base of the big toe is very susceptible to sodium urate accumulation, although the salt builds up at other joints also. Painful inflammation results, when cells of the immune system engulf the sodium urate crystals. Urate crystals may also appear as kidney stones and lead to painful obstruction of the



Scheme 5: Mechanism of uric acid production in mammals

urinary tract. Administration of allopurinol (**45**), a purine drug and an analogue of hypoxanthine, is an effective treatment for gout. The mechanism of action of allopurinol is quite interesting: it acts first as a substrate and then as an inhibitor of xanthine oxidase. The enzyme xanthine oxidase hydroxylates (**Scheme 6**)



Scheme 6: Hydroxylation of allopurinol by xanthine oxidase

allopurinol to alloxanthine (**46**), which then remains tightly bound to the active site of the enzyme, an example of suicide inhibition. Once the active sites of the enzymes get blocked, synthesis of urate from hypoxanthine and xanthine becomes lower and thus serum concentrations of hypoxanthine and xanthine raise, while that of urate drops. However, hypoxanthine and xanthine do not accumulate to harmful concentrations because they are more soluble and thus more easily excreted.

1.3.2 As adenosine receptor antagonist

Adenosine receptors are established as important pharmacological target for the treatment of variety of diseases such as anti-inflammatory conditions, sepsis, heart attack, asthma, diabetes, obesity and Parkinson's disease [20]. Four adenosine receptors (ARs) viz. A_1, A_{2A}, A_{2B} and A_3 have already been cloned and pharmacologically characterized till now and all of them are found to belong to the super family of G protein-coupled receptors [21]. There are now accumulating evidences that specially designed adenosine receptor antagonist to a particular subtype may provide an efficient therapeutic treatment to a particular disease. In this regard, numerous pyrimidine derivatives have been established as efficient adenosine receptor antagonists. In fact, xanthine derivatives have represented the most potent class of adenosine receptor antagonists [22]. As such, a flurry of reports has been found manifesting the importance, role and effectiveness of pyrimidine based compounds as inhibitors of various adenosine receptors [23]. 8-Phenytheophylline (**47**, **Fig. 11**) represents the parent member of numerous potent adenosine receptor antagonists and variation of substituents and their position on the phenyl ring lead to change in potency and selectivity towards adenosine receptors as well as the water solubility. Bansal, R. et al. [23a], in their work, carried out an elaborate study on the effect of substituents and their positions in the 8-phenyl ring of **47** upon potency and selectivity at A_1 and A_{2A} adenosine receptors. Among the compounds tested, they found 1,3-dimethyl-8-[4-methoxy-3-(2-morpholin-4-ylethoxy)phenylxanthine (**48**) as the most potent and selective towards A_{2A} AR subtype with K_i= 100 nM over A_1 receptor (K_i> 100 mM).

6-carbethoxy-1,2,3,4-tetrahydro-1,3-dimethyl-5-(2-naphthylmethyl)aminopyrido[2,3-*d*]pyrimidine-2,4-dione (**49**) [23b], a non-theophylline pyrimidine derivative has been found 300 fold more potent than the lead compound, N^5-butyl-6-cyano-1,3-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4-dione (**50**) towards A_{2A} receptor. 8-(4-(3,6,9,12-tetraoxatricos-22-enyloxy)phenyl)-theophylline (**51**, **Fig. 12**), an oligo(ethylene glycol)-alkene substituted theophylline has been reported [23c] as high affinity (K_i= 4.06 nM) human A_{2B} receptor antagonist with 24.1 fold selectivity (K_{iA2A}/K_{iA2B}= 24.1) versus human A_{2A} receptor with a water solubility of 1mM. Elzein, E. et al. have been working in the field of development of pyrimidine based nontheophylline compounds as A_{2B} AR antagonist and have reported [23d-g] considerable numbers of such compounds. Among those, 8-(1-(3-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-3-ethyl-1-propyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**52**, **Fig. 12**) displays high affinity (K_i= 22 nM) and selectivity for the human A_{2B} AR relative to A_1, A_{2A} and A_3 ARs. The compound

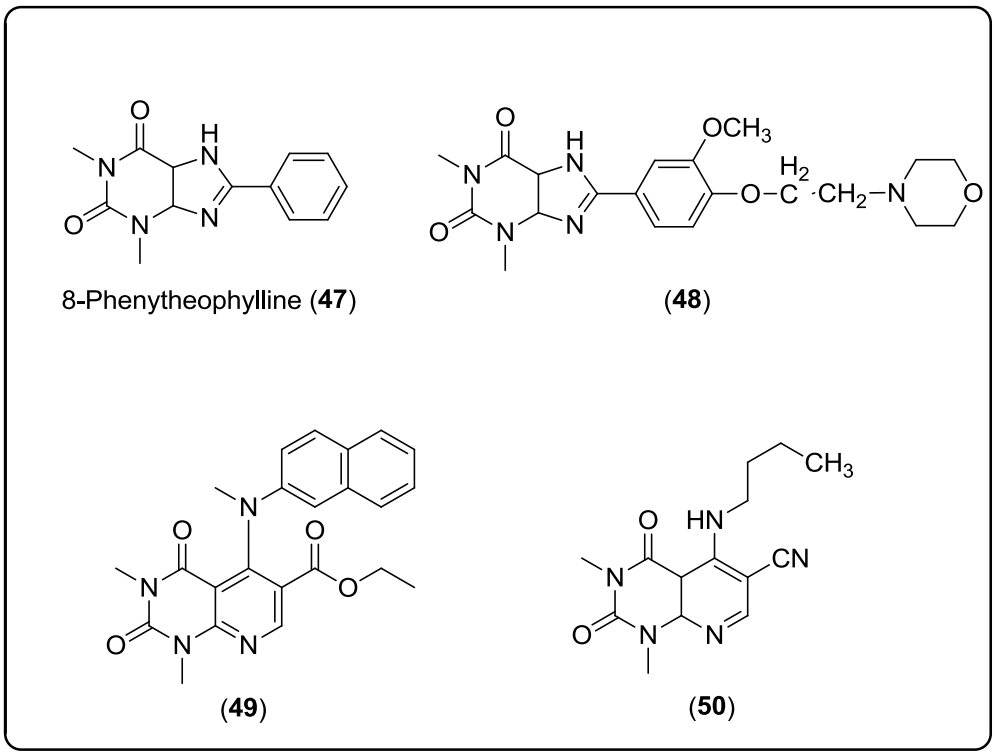


Fig. 11: Structures of **47**, **48**, **49** & **50**

is found to be well tolerated and without having serious adverse effect in a single ascending dose phase I clinical study which might be an answer to the effect of A_{2B} AR antagonism on chronic inflammatory lung diseases in near future. Elzein, E. et al. have reported [23h] two A_1 AR antagonists (**53** & **54**) also with high affinity and selectivity over A_3 and A_{2A} ARs. While **53** displays K_i= 1 nM for A_1 AR and >5000-fold selectivity over A_3 and A_{2A} ARs, the values are 0.6 nM and >600 respectively for **54**. Many pyrimidine derivatives are found as active antagonist to A_3 adenosine receptor. In their works, Yaziji, V. et al. has reported [23i] four A_3 adenosine receptor antagonists (**55**, **56**, **57** & **58**), possessing remarkable activity (Ki< 10 nM) against it, but noticeably no activity against all other adenosine receptors.

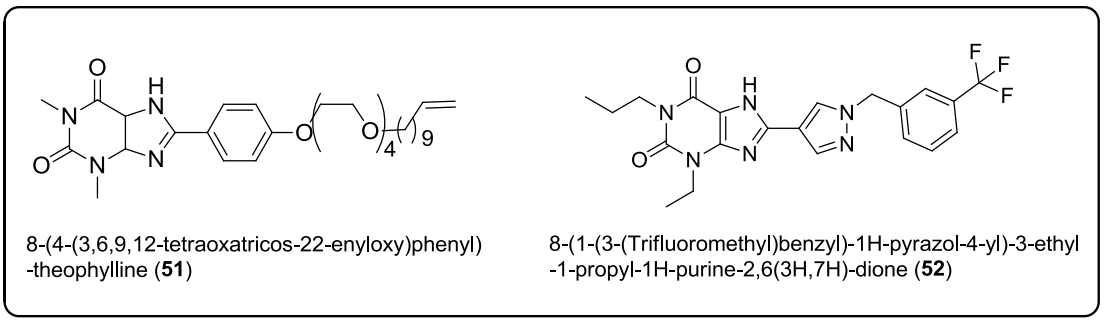


Fig. 12: Selective A_{2B} adenosine receptor antagonists

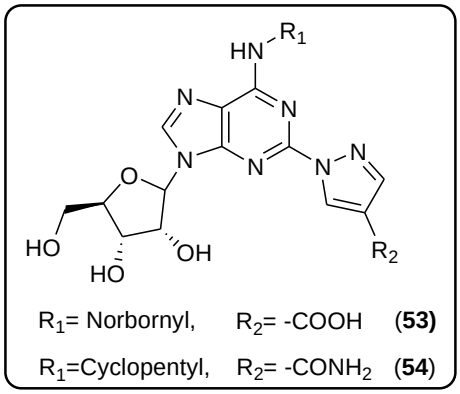


Fig. 13: Selective A_1adenosine receptor antagonists

1.3.3 As monamine oxidase B inhibitor

Parkinson's disease is a degenerative disorder of the central nervous system, which is mainly caused by the loss of dopaminergic neurons of the substantianigria

located at the midbrain. Monamine oxidase B (MAO-B) is found as an important target for the development of new anti-Parkinson's drugs and Monoamine oxidase-

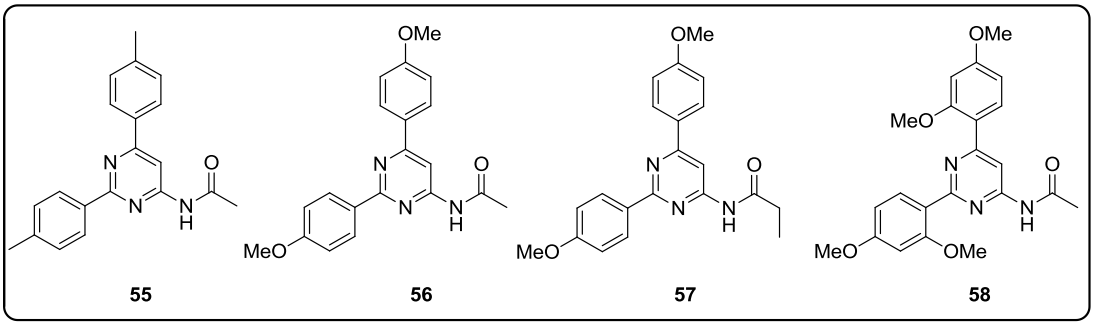


Fig. 14: Selective A_3 adenosine receptor antagonists

B (MAO-B) inhibitor has been used as neuroprotectants to treat the motor deficits of Parkinson's disease.The enzyme MAO-B, located in the mitochondrial outer membrane plays an important role in the metabolism of dopamine and neuroactive and vasoactive amines in the central nervous system. Inhibition of this enzyme enhances the elevation of dopamine levels in adjunctive treatment with levodopa [24], and delays the onset of relapse following levodopa monotherapy [25]. Studies

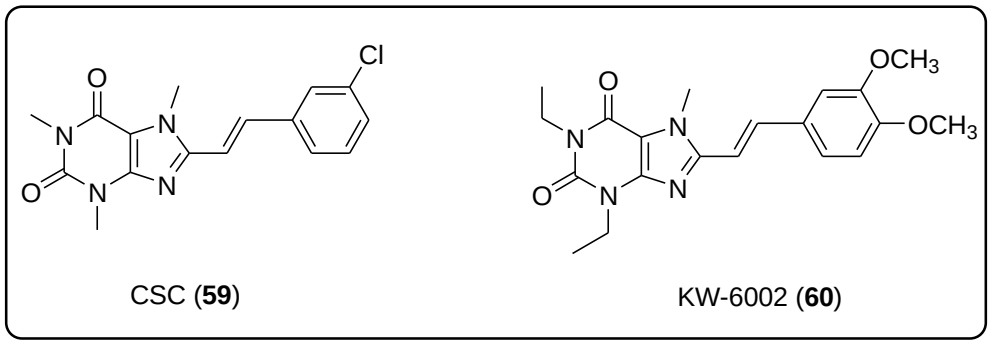


Fig. 15: Structure of MAO-B inhibitors

towards the development of MAO-B inhibitor suggested the importance of nitrogen containing heterocycle in the structural feature [26] which prompted researchers to choose caffeine, or xanthine and theophylline, as the core structure of the compound to design potential MAO-B inhibitor. As such, *(E)*-8-(3-Chlorostyryl) caffeine (CSC, **59**) and KW-6002 (**60**) have been reported as inhibitors of MAO-B with a K_i value (enzyme inhibitor dissociation constant) of 128 nM and 11 μM,

respectively [27]. Study towards the structure activity relationship has shown that substitution at C-8 of caffeine with an electron deficient group produces a higher affinity monamine oxidase B inhibitor. The study has also revealed the importance of the *trans* configuration of the styryl double bond and the substitution pattern at the xanthine ring. However, the *trans* double bond, being sensitive to light undergoes isomerization to its *cis* counterpart which is expected to be inactive against MAO-B. To avoid this shortcoming, Song et al. has designed a new class of pyrimidine based MAO-B inhibitor in which the double bonds are replaced by

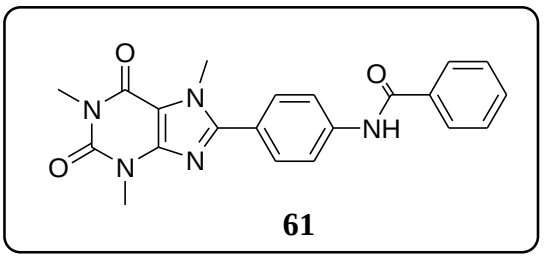


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Fig. 16: Structure of **61**

diaryl amide units, among which **61** has been found to have 42-fold activity than the lead compound KW-6002 [28]. Numerous other CSC and KW-6002analogs have also been designed, synthesized and found to possess high affinity versus MAO-B [29].

1.3.4 As antibacterial

The worldwide emergence over the past three decades of bacterial strains resistant to most current antibiotics raises a serious threat to global public health [30]. After several decades of continuously successful antibiotic therapy against bacterial infections, we are now really in trouble due to the accelerated evolution of antibiotic resistance to important human pathogens and the scarcity of new anti-infective drug families under development. Efflux is a general mechanism responsible for this bacterial resistance to antibiotics [31]. So, inhibition of bacterial efflux mechanisms now becomes a promising target in order to (i) increase the intracellular concentration of antibiotics that are expelled by efflux pumps, (ii) restore the drug susceptibility of resistant clinical strains, and (iii)

reduce the capability for acquired additional resistance. A flurry of structurally unrelated classes of efflux pump inhibitors (EPIs) have been described and tested in the last two decades, including some analogues of antibiotic substrates and new chemical molecules. The need for novel antibiotic classes to combat bacterial drug resistance has led to considerable efforts to identify and exploit new antibacterial targets and novel antimicrobial agents.

A large number of pyrimidine derivatives possessing antibacterial activity have been reported every year and some of them are in clinical trial. In Nature Reviews Drug Discovery [32], M. H. Flight highlighted the work of Stover and colleagues [33] screening of Pfizer compound library of 1.6 million compounds for antibacterial activity resulting the discovery of three pyrido[2,3-*d*]pyrimidine (**62**, **63** & **64**) derivatives as potent synthetic antibacterial that targeted the bacterial biotincarboxylase selectively. They made a particular note of their exquisite potency against clinical isolates of fastidious Gram negative pathogens such as *Haemophilus influenza* and *Moraxella catarrhalis*; causative agents of many respiratory tract infections. This series of pyridopyrimidines target the ATP-binding site of biotin carboxylate (BC) in the bacteria which catalyzes the first step of fatty acids biosynthesis. The fact that these compounds can selectively target the

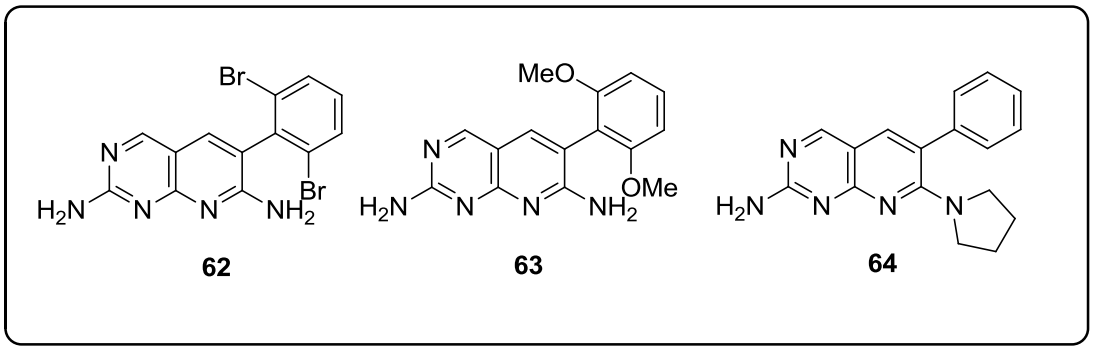


Fig. 17: Structures of **62**, **63** & **64**

BC inspite of having considerable structural similarity to eukaryotic protein kinases including human kinases is established. In their report [31], Zega, A. et al. demonstrated 6-Aryl-pyrido[2,3-*d*]pyrimidines as novel ATP-competitive inhibitors of bacterial D-alanine: D-alanine ligase and established a mechanism for

their antibacterial activity. The bacterial enzyme D-alanine: D-alanine ligase (Ddl) catalyzes the ATP-dependent formation of a dipeptide D-Ala-D-Ala that subsequently takes part in the biosynthesis of disaccharide-pentapeptide peptidoglycan structure, which is a specific and essential component of the bacterial cell wall. 6-arylpyrido[2,3-*d*]pyrimidines target this bacterial enzyme and bind tightly to it by competing with ATP and thereby inhibits the formation of D-Ala-D-Ala. 4-((4-chlorophenyl)thio)-1-(pyridin-3-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**65**), a thiopyrazolo[3,4-*d*]pyrimidine derivative has been reported to exhibit in vitro anti-microbacterial activity (MIC< 2 mg/mL) that is comparable to clinically used drugs like ethambutol (**66**) (MIC= 2 mg/mL) coupled with no cytotoxicity against a HepG2 cell line [34]. Numerous other pyrimidine derivatives have been synthesized and demonstrated active against various Gram-positive and Gram-negative bacteria with moderate to excellent efficiency [35].

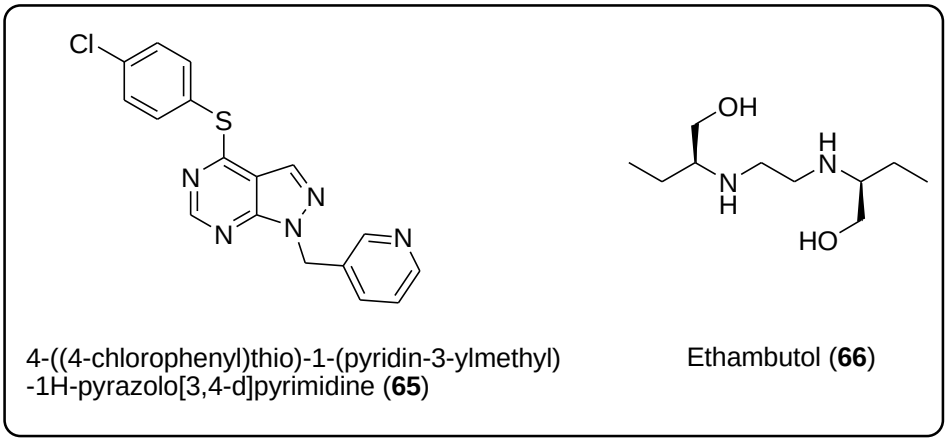
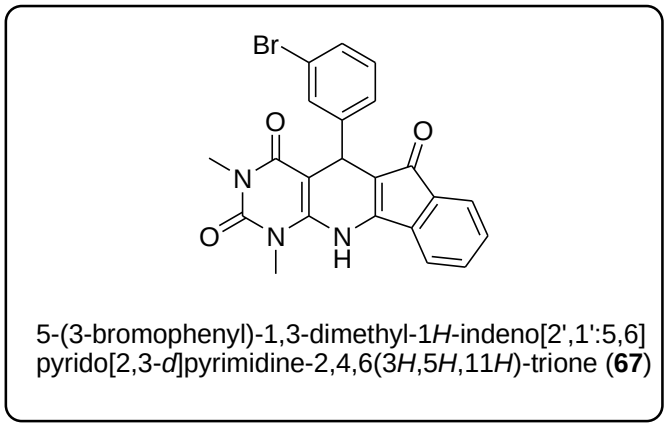


Fig. 18: Thiopyrazolo[3,4-*d*]pyrimidine antibacterial (**65**) & Ethambutol (**66**)

It is reported that diarrhea is responsible for 2.5 million deaths per year of children in the developing countries [36], and enterotoxigenic strains of bacteria including *Escherichia coli* are responsible for about 60% of this mortality rate [37]. Kots, A. Y. et al. carried out a study to screen a compound library against enterotoxigenic strains of *Escherichia Coli* and identified a pyridopyrimidine derivative (**67**) as a promising lead compound for treatment of diarrhea and other disease caused by enterotoxigenic strains of bacteria [38].



5-(3-bromophenyl)-1,3-dimethyl-1*H*-indeno[2',1':5,6] pyrido[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,11*H*)-trione (**67**)

Fig. 19: Promising drug for diarrhea

1.3.5 Antiviral agent

Numerous pyrimidine derivatives have been found effective against various viruses and some of them are in clinical use. Simple examples include *Adefovir* (**68**) and *Tenofovir* (**69**) [39], both are prescription medicines used to treat infections with hepatitis B virus. In fact, *Tenofovir* is on the world health organization's list of essential medicines, a list of the most important medicines needed in a basic health system. Although, both *Adefovir* and *Tenofovir*are nucleotide analog reverse transcriptase inhibitors (ntRTIs) that block reverse transcriptase, a crucial virus enzyme in human immunodeficiency virus 1 (HIV-1) and hepatitis B virus infections, *Adefovir* is a failed treatment for HIV while *Tenofovir* is effective against HIV-1. Due to high mortality and morbidity rate, HIV infection is a huge challenge to today's scientific community. Despite tremendous efforts [40], effective HIV vaccine remains elusive till date and chemotherapy continues to provide the main leverage in battling HIV/AIDS. The most standard therapy currently in used is the highly active antiretroviral therapy (HAART) [41], which involves the use of multiple antivirals with orthogonal mechanisms of action to create a large genetic barrier to resistance. However, drug-drug interactions bring complication to HAART [42]. As such, the simplest and efficient form of multi-target therapy would be a single structure compound inhibiting multiple viral targets. In this connection, Wang, Z. et al. have been contributed considerably to design and synthesize pyrimidine based compounds possessing inhibitory activity to both HIV-1 reverse

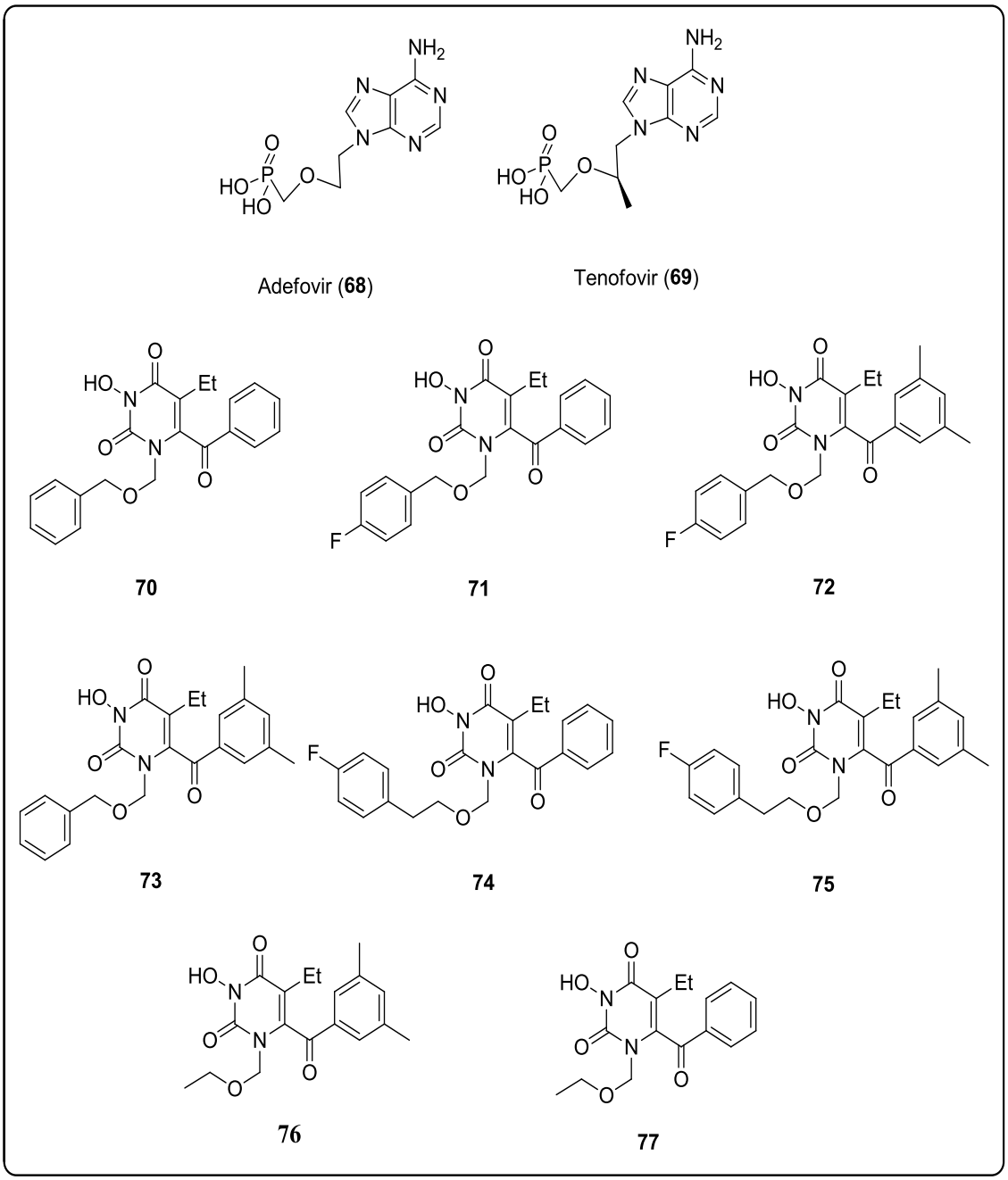


Fig. 20: Structures of some anti-HIV compounds

transcriptase (RT) and integrase (In) [43]. Some examples of such compounds are shown in **Fig. 21**. While compound **74** and **77** are found selective against HIV-1 IN and RT respectively, the rest of the compounds in **Fig. 21** possess dual activity against both of them [44]. In their report [45], Hocková, D. et al. demonstrated two pyrimidine based nucleoside inhibitors (**78** & **79**) with potency against HIV

(0.0027-0.011 mmol/mL) which is comparable to that of *Adefovir* and *Tenofovir*. A series of *N*-1-alkylated-5-aminoaryalkylsubstituted-6-methyluracil have been designed, synthesized and evaluated as potential non-nucleoside HIV-1 RT inhibitors [46], among which compounds **80**, **81**, & **82** (**Fig. 22**) are found to possess potency comparable to clinically used drug *Nevirapine*(**83**).

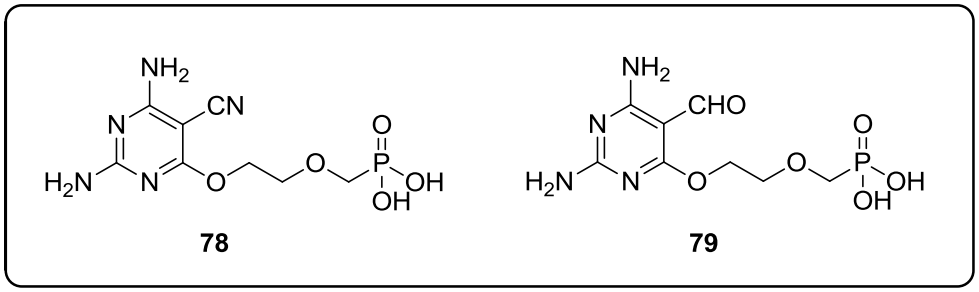


Fig. 21: Potential antiretroviral agents

Hepatitis C virus (HCV) is the culprit associated with majority of chronic hepatitis infections and a major cause of liver disease and transplantations worldwide. The infection is highly persistent and still lacks a well-tolerated antiviral therapy [47]. Varaprasad, C. V. N. S. et al. have reported [48] the synthesis of a series of

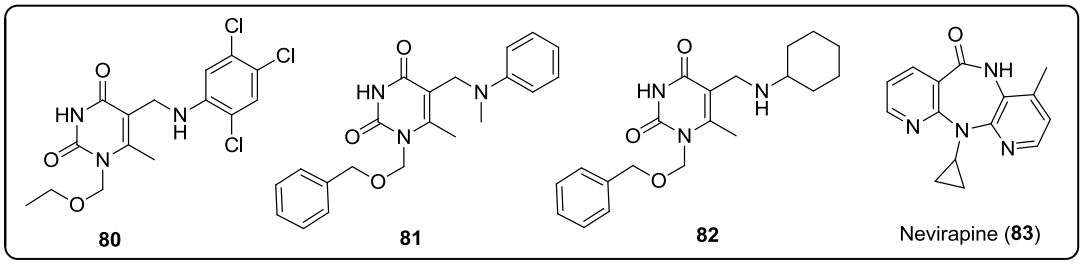


Fig. 22: Non-nucleoside HIV RT inhibitors

pyrrolo[2,3-*d*]pyrimidine nucleoside derivatives among which three compounds (**84**, **85** & **86** in **Fig. 23**) have been found to possess good activity and selectivity to inhibit HCV RNA.

Dengue virus is another pathogenic virus for which no significantly effective drugs or vaccines have been developed till date. There are very few compounds known to inhibit the replication of this virus. Nair V. et al. has developed a heterocyclic

molecule (**87**) having a pyridopyrimidine core which is reported to possess a significant activity against dengue virus [49].

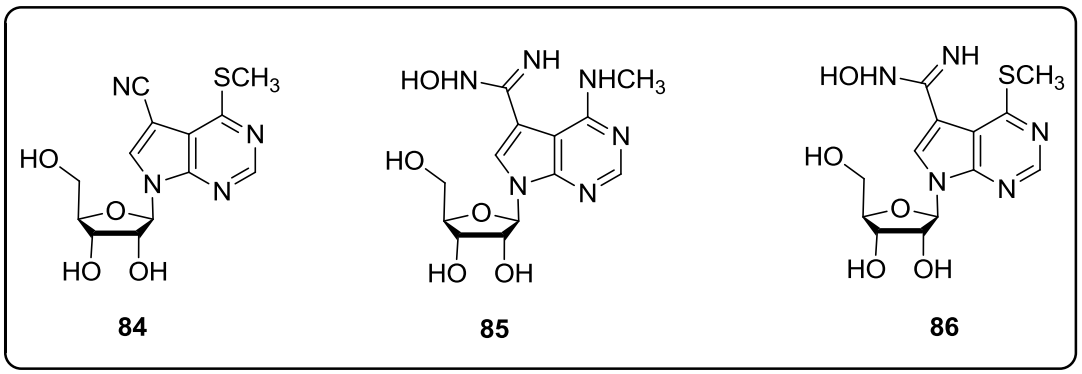


Fig. 23: Selective HCV inhibitors

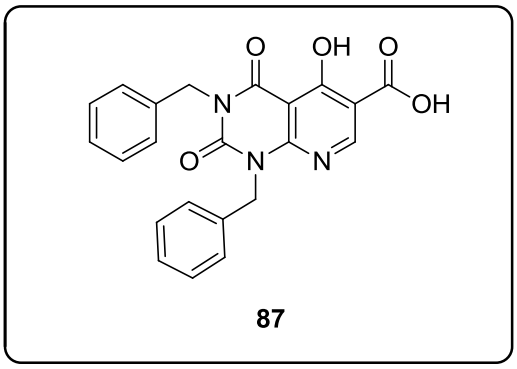


Fig. 24: Pyrido[2,3-*d*]pyrimidine derivative with activity against dengue virus

1.3.6 Antitumor and anticancer agent

For a cell to reproduce, it must first faithfully replicate the entire DNA in its genome. During DNA synthesis, purine and pyrimidine molecules must be made available to allow for the synthesis of the nucleotide building blocks and ultimately the new DNA molecules. A reduction in the availability of the raw materials needed to build DNA leads to stoppage of DNA synthesis and inhibition of cell division. Various pyrimidine derivatives have been found effective to inhibit cell division via different mechanisms and so are considered as potential anticancer agents. A very simple pyrimidine derivative, 5-Fluorouracil (**88**) [50] is a marketed anticancer drug in trade names of *Adrucil*, *Carac*, *Efudex* and *Efudix*. Alimta (Pemetrexed, **89**),

(*S*)-2-(4-(2-(2-amino-4-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl)benzamido)pentanedioic acid is a much talked antineoplastic antifolate [51] due to its remarkable activity against a broad spectrum of solid tumors. The compound was first prepared to examine the biochemical consequences of removing C-6 stereogenic center of lometrexol (**90**), which had been known for its antitumor activity [52]. Further studies confirmed the antitumor activity of pemetrexed via mechanisms different from lometrexol [53]. It is found as a new generation multi targeted antifolate that inhibits several key enzymes in the *de novo* pathways of pyrimidine and purine biosynthesis, including thymidylate synthase (TS), dihydrofolatereductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT) [54]. Its antitumor activity has been found to cover a broad array of human malignancies, e.g. breast, non-small cell lung cancer,

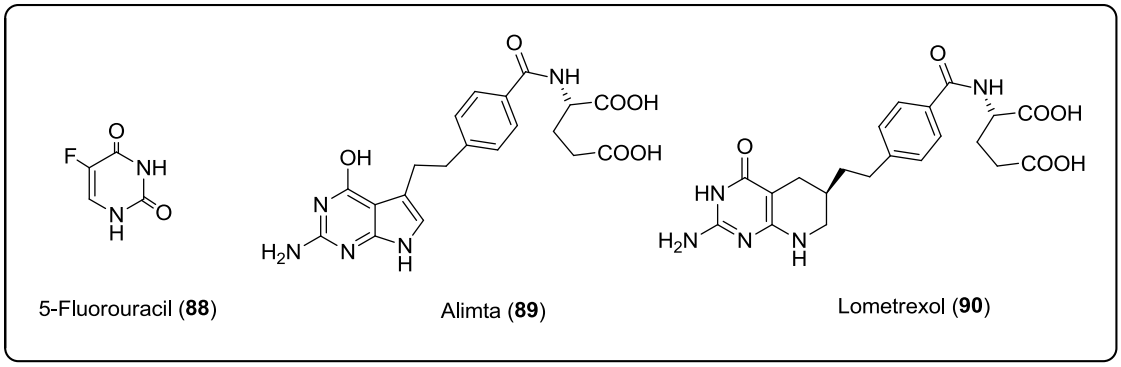


Fig. 25: Structures of some anticancer agents

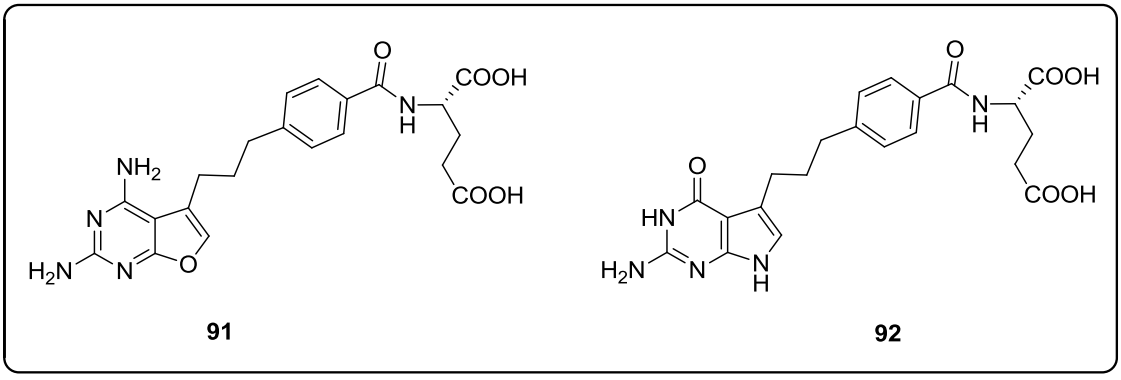


Fig. 26: Antitumor active furopyrimidine (**91**) and pyrrolopyrimidine (**92**) derivative

malignant pleural mesothelioma and pancreatic, colorectal, gastric, bladder, head and neck cancer, and is currently in phase III clinical trials [55]. Numerous attempts have been made to synthesize alimta analogs and to evaluate their antitumor activity. Gangjee, A. et al. has reported two such compounds **91** & **92** with activity comparable to alimta. While **91** is a furo[2,3-*d*]pyrimidine derivative, **92** is a pyrrolo[2,3-*d*]pyrimidine derivative [56]. Two other pyrrolopyrimidine derivatives **93** & **94** are also found to have significant antitumor activity and found active against the full tumour human cell line panels [57]. Thymidine phosphorylase (TP) has been associated with tumor progression and metastasis and various pyrimidine derivatives are found effective as inhibitors of humanthymidine phosphorylase. **Fig. 28** demonstrates some pyrimidine derivatives (**95**, **96** & **97**) with TP inhibitory activity [58]. Ma, L.-Y. et al. has designed, synthesized and evaluated the anticancer activity of a series of novel

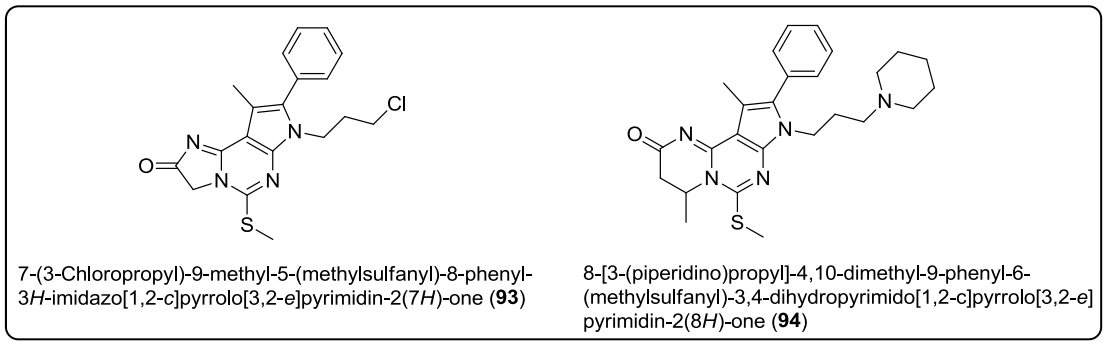


Fig. 27: Antitumor active pyrimidine derivatives

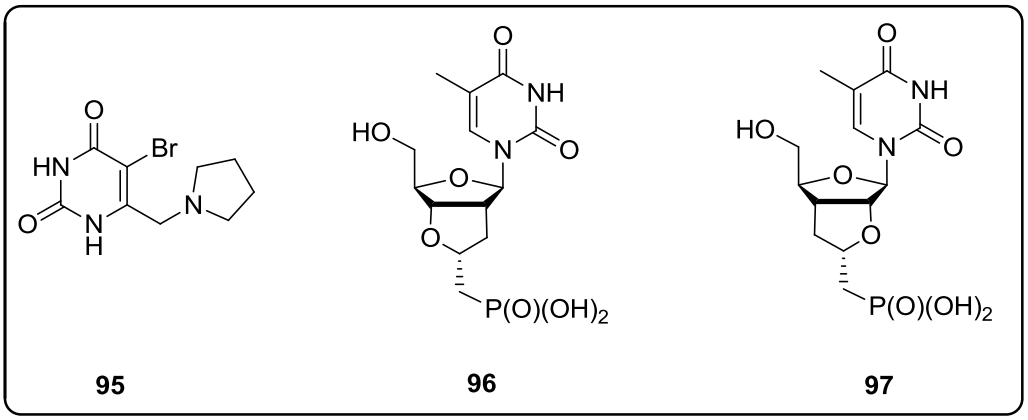


Fig. 28: Pyrimidine derivatives as thymidine phosphorylase inhibitor

1,2,3-triazole-pyrimidine against four selected cancer cell lines (MGC-803, EC-109, MCF-7 and B16-F10), one of which is found to have excellent anticancer activity with single-digit micromolar IC_{50} values ranging from 1.42 to 6.52 μM [59].

1.3.7 Anti-inflammatory agents

A flurry of reports [60] including patents [61] has been obtained depicting the anti-inflammatory nature of pyrimidine derivatives. It is reported that Phophodiesterase 4 (PDE4) is expressed in inflammatory and involves in the hydrolysis of cyclic adenosine monophosphate (cAMP) [62]. An up-regulation of cAMP suppresses the inflammatory responses and so PDE4 has been targeted for the treatment of inflammatory diseases. Goto, T. et al. have recently reported a pyrano[3,2-*d*]pyrimidine (**98**) as a highly potent and selective PDE4B inhibitor, having human PDE4B inhibitory activity with an IC_{50} of 3.0 nM and 433 fold PDE4B selectivity over PDE4D [63]. Baraldi, P. G. et al. has demonstrated another promising approach for treatment of inflammation by developing a series of pyrimidine based antagonists of the transient receptor potential ankyrin 1

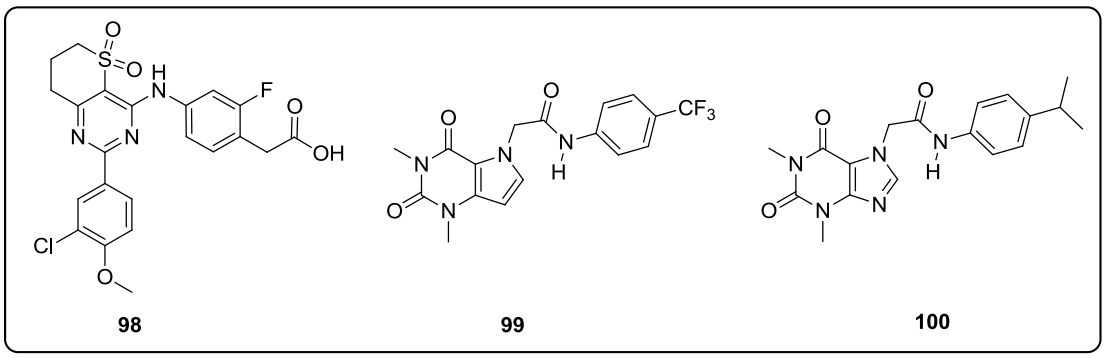


Fig. 29: Some pyrimidine based anti-inflammatory compounds

(TRPA1) channel. They have identified a compound **99**, which shows remarkable improvement in potency (IC_{50}= 400 nM) against human TRPA1 with regard to the reference compound (**100**) [64]. In their report, Sondhi, S. M. et al. have reported three other pyrimidine derivatives (**101**, **102** & **103**) exhibiting anti-inflammatory activity comparable to standard drug ibuprofen [65].

Numerous other pyrimidine derivatives have been found to possess a wide variety of medicinal values and those are demonstrated in various reviews [66].

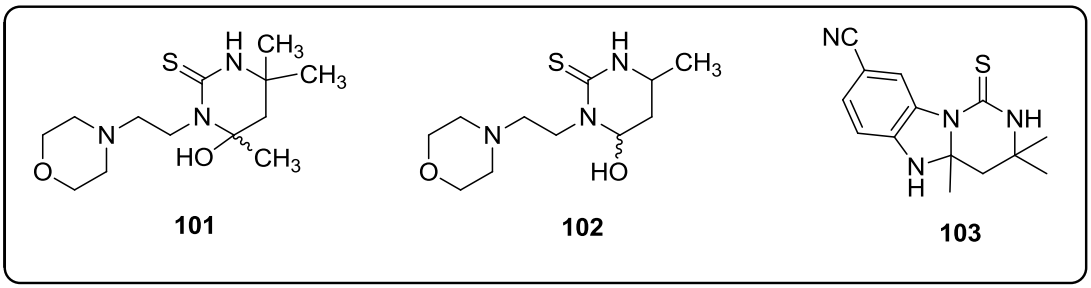


Fig. 30: Pyrimidine base anti-inflammatory compounds

1.4 In material chemistry

Besides its never ending importance in biological and medicinal research, the pyrimidine scaffold has been able to attract attention of the material chemists also in recent times. The scaffold has got enough space in research regarding design and synthesis of liquid crystals [67]. Recently, Rahman et al. reported a pyrimidine based bent core liquid crystal monomer (**104**), which can be used for preparation of polymers or silyl functionalized bent-core mesogens. The presence of azo linkage imposes photo-switching property to the monomer as it undergoes *cis-trans* isomerization under UV irradiation [68]. Pyrimidine has marked its existence in fluorescence chemistry also, particularly by its utility to study DNA-folding and recognition via the synthesis and application of fluorescent nucleoside [69]. Srivatsan, S. G. et al. reported a furan-containing fluorescent ribonucleoside (**105**)

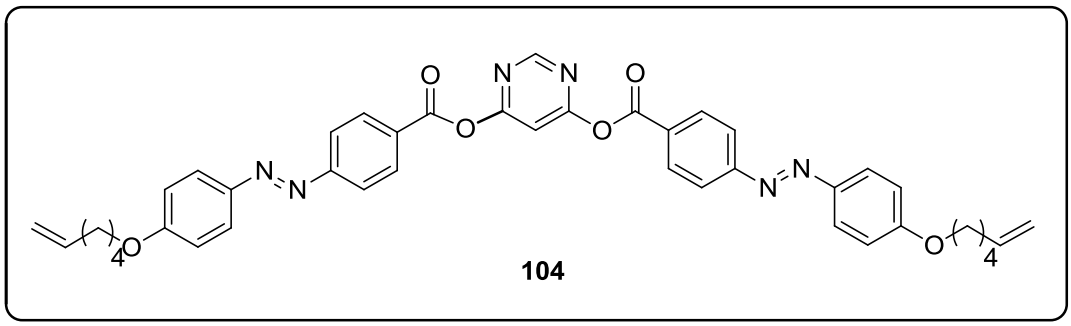


Fig. 31: Pyrimidine based photo-switchable bent-core liquid crystal monomer

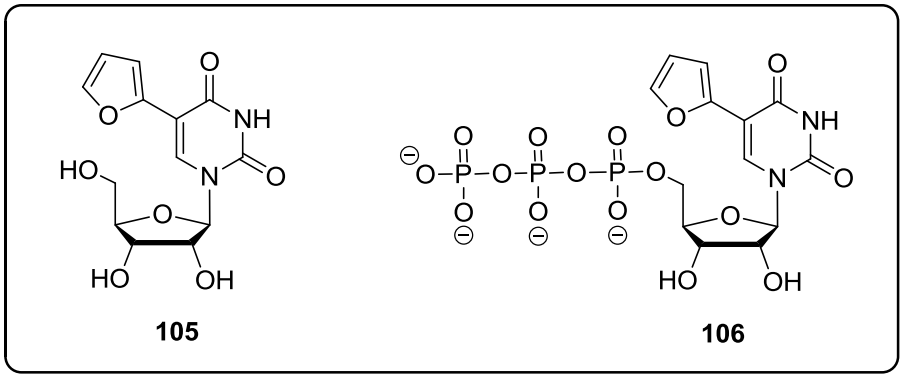
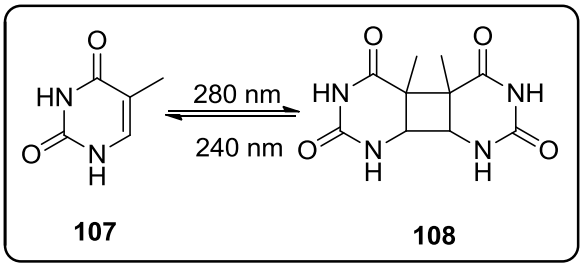


Fig. 32: Fluorescent ribonucleoside (**105**) and its triphosphate (**106**)

and its triphosphate (**106**) and demonstrated that the enzyme T7 RNA polymerase accepts the fluorescent ribonucleoside triphosphate as substrate in *in vitro* transcription reactions and very efficiently incorporates it into RNA oligonucleotides, generating fluorescent constructs [70]. The binding of this RNA target to aminoglycoside antibiotics can be effectively monitored by fluorescence spectroscopy which paves the way for a potential therapeutic utility. Relying on the reversible photodimerisation of pyrimidine ring (**Scheme 7**), Patra, A. et al. demonstrated that pyrimidine derivative with thiol-terminated hydrocarbon chains form photo responsive self-assembled monolayer on smooth gold surfaces,



Scheme 7: Photodimerization of thymine

which can be used to reversibly control the wettability of the surface [71]. Dimerization of pyrimidine rings take place when irradiated with light of wavelength 280 nm while the reverse process takes place under irradiation with light of 240 nm wavelength. The redox property of some of the pyrimidine derivatives has also been investigated. Naya, S. -i. et al. reported a convenient preparation of pyrimidine based cations (**109**, **110**, **111** & **112**) and studied their

redox properties [72]. In fact, they carried out reduction of carbonyl compounds (**Scheme 8)** using these cations with their hydride adducts, an attempt to copy the NAD^+-NADH model of reduction of pyruvate. In their work, Gutiérrez-Valero, M. D. et al. studied the adsorption of specially designed pyrimidine based ligand and in fact became successful to remove Cu (II) ions from aqueous solution using the adsorbed material [73].

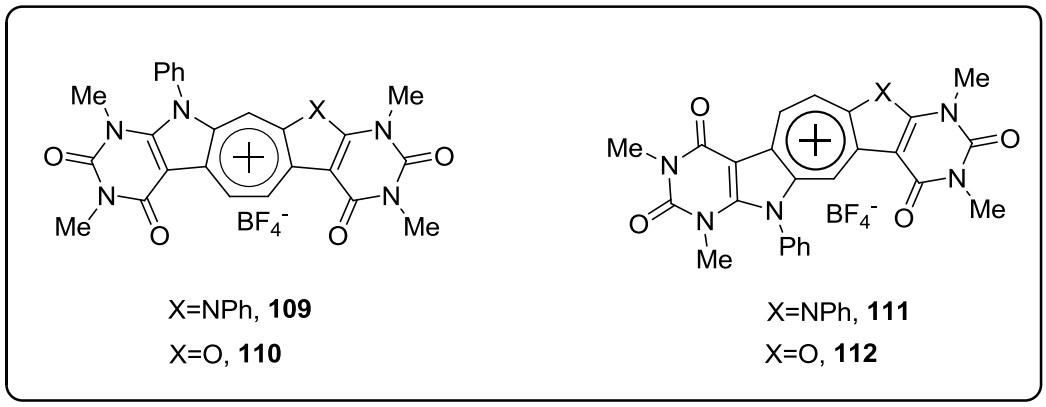
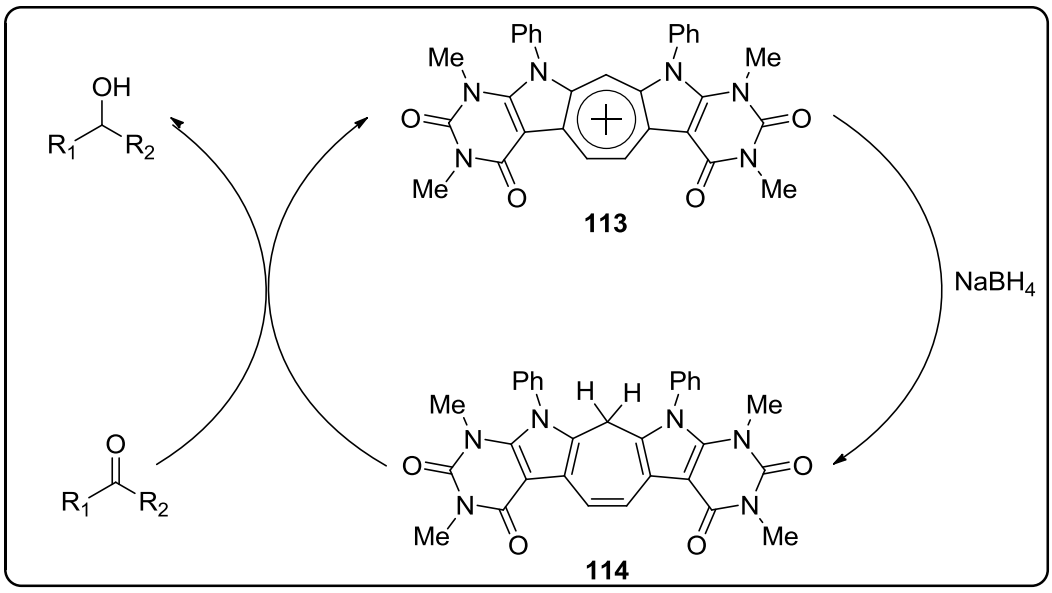


Fig. 33: Pyrimidine based compounds with redox property



Scheme 8: Redox activity of pyrimidine based compound

Due to the immense biological, medicinal as well as material significances of pyrimidine derivatives, synthetic chemists have also been putting their best effort

to develop novel, efficient methodology for various structurally important pyrimidine scaffolds. Hundreds of reports have been published every year describing and demonstrating the need and usefulness of newer methods. These synthetic routes will be discussed in their relevant chapters.

Feeling the ever-increasing vitality, demand and specially considering the bioactivity of this attractive moiety, we have targeted to synthesize structurally important derivatives of pyrimidine scaffolds and set the following objectives:

I. To develop novel and efficient methodology for synthesizing structurally important pyrimidine derivatives.
II. To promote economical and environmentally friendly experimental procedures (green chemistry).
III. To study the side selectivity and regioselectivity of the reactions.

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